

**Case Report**

Open Access, Volume 4

**Management of central hyperthermia in traumatic brain injury using baclofen: A case report****Gaurav Gomez<sup>1</sup>; Ijaz N Pillai<sup>2\*</sup>**

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Received: Dec 23, 2022

Accepted: Jan 17, 2023

Published: Jan 24, 2023

Archived: [www.jcimcr.org](http://www.jcimcr.org)

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DOI: [www.doi.org/10.52768/2766-7820/2254](https://doi.org/10.52768/2766-7820/2254)

**Abstract**

**Background:** Central hyperthermia in CNS disorders is often misdiagnosed or under diagnosed due to inadequate data. Current diagnosis is one of exclusion. Existing treatment modalities as per guidelines are symptomatic and supportive. Fever after Traumatic brain injury may worsen functional outcome and prolong hospital stay, hence need to be evaluated and treated promptly.

**Case:** We discuss a case of a 33-year-old gentleman with traumatic brain injury with prolonged fever spikes during rehabilitation. The hyperthermia was non-responsive to antipyretics and antibiotics. A diagnosis of central hyperthermia was reached after eliminating other causes.

Based on a prior case report Baclofen was tried to manage central hyperthermia. A complete cessation of fever was noted within 2 days of initiation. The corresponding decrease in temperatures and days of Baclofen administration followed by recurrence with cessation, are depicted graphically. Once baclofen was resumed, he remained afebrile. This case brings to light the possible efficacy of low dose Baclofen in the management of fever of central origin. It also highlights the unusual presentation of fever of central origin in the sub-acute stage after traumatic brain injury.

**Conclusion:** Baclofen may have a role in management of central hyperthermia. Future studies to evaluate the efficacy and side effects of Baclofen in its management during acute and subacute period are warranted. Standardization of its use with well-designed clinical trials is the proposed next step.

**Keywords:** Fever; Traumatic brain injury; Rehabilitation; Baclofen; Neurological rehabilitation; Pyrexia.

## Introduction

Central hyperthermia in CNS disorders is a peculiar and often misdiagnosed or underdiagnosed condition due to the inadequate data available. After a Traumatic Brain Injury (TBI), fever occurs due to multiple reasons especially in the acute phase in the intensive care system or during sub-acute rehabilitation.

Appropriate detection of the cause of fever is vital for its management, which helps reduce hospital stay duration, morbidity and prevent breaks in rehabilitation.

Approximately 70 percent of TBI patients in the ICU exhibit fever. More than 50% of such cases have fever due to an infective pathology [1]. Once an infective origin has been ruled out through appropriate investigations, a central thermoregulatory dysfunction may be considered.

Damage to the diencephalon, either traumatic or non-traumatic has been shown to cause central hyperthermia. Hypothalamus has been associated with central hyperthermia in previous studies [2,3].

Existing guidelines by American Heart Association and American Stroke Association of 2013 for the management of central hyperthermia are mainly supportive. Antipyretic therapy has been advised for temperature  $>38^{\circ}\text{C}$  (class I, grade C recommendation) [4]. European guidelines recommend aggressive methods to control fever such as sand body-conformed wraps, intravascular cooling devices, head-only cooling caps, or inhaled perfluorocarbon cooling systems to attain normothermia (class II A, grade B recommendation) [5].

Antipyretics have been shown to be inconsistently effective in central hyperthermia. Other supportive measures such as internal or external cooling devices have been advised. Previous case reports have documented promising results with drugs such as Bromocriptine [6] and Baclofen [7].

In this paper we discuss the case of a 33-year-old gentleman, with a TBI injury who had high fever spikes during rehabilitation.

## Case presentation

A 33-year-old gentleman with no known comorbidities had a road traffic accident on the 31st of May, 2020. He sustained a trauma to the brain, following which he lost consciousness and was brought to the Emergency Department of a tertiary care hospital in Karnataka. At presentation, his GCS was E1M2V4. He was intubated and mechanically ventilated in view of low GCS. Initial CT brain imaging. (1/6/2020) showed hemorrhagic contusion of the left cerebral peduncle, left midbrain and right superior cerebellar peduncle. He also had a mild Sub arachnoid hemorrhage in the left frontal region.

In view of prolonged ventilation, he was tracheostomized on 11th day of admission. He regained consciousness after the 14th day and was shifted out of ICU after 15th day. During the ICU stay, he developed multiple fever spikes which was attributed to a Lower Respiratory Tract Infection (LRTI). This was managed with culture specific antibiotics. Once the patient was afebrile and medically stable, he was taken over for in-patient rehabilitation by our Department of Physical Medicine and Re-

habilitation (PMR).

On admission to PMR (Day 1 of PMR stay), he was in Minimally Conscious State (MCS), and had altered sleep cycles. He was on a Ryle's tube for feeding, he was breathing through a Tracheostomy tube, and had an Indwelling urinary catheter.

The patient was noticed to have Paroxysms of Sympathetic Hyperactivity, presenting with hyperthermia, hypertension, tachycardia, tachypnoea and dystonia. The temperature charts showed readings ranging from  $98-99^{\circ}\text{F}$ . According to departmental protocol, he was started on Tablet Propranolol, a non-selective beta blocker, with which these symptoms and signs subsided completely. Patient remained afebrile for the following 3 days.

On PMR day 3, he developed sudden onset high grade fever. An infectious etiology was suspected. Symptomatically he was treated with Intravenous paracetamol, following which the fever reduced transiently. Tepid sponging with cold water was also included in his fever management.

Blood investigations for malaria, filarial parasite and dengue were negative. Total Leucocyte Count (TLC) was serially found to be normal. Neutrophilia was however noted. Serum procalcitonin was normal.

Although blood culture yielded no growth (day 6), tracheal trap aerobic culture showed presence of Methicillin Resistant Staphylococcus Aureus (MRSA) and Acinetobacter series. He did not have features suggestive of upper or lower respiratory tract infection. After a cross-consultation with the Department of General Medicine, Inj. Colistin 4.5 g twice daily and Inj. Vancomycin 1 g were given intravenously twice daily.

His TLC continued to remain within normal limits. He continued to have fevers even after 10 days of antibiotics. After a review with Dept of General Medicine, the antibiotics were continued for a total of 15 days. Due to continuing fever, blood culture was done after giving 1 week of injectable antibiotics and showed no growth. Relevant blood reports are tabulated below (Table 1).

**Table 1:**

Date	Day 4	Day 5	Day 8	Day 11	Day 13	Day 17	Day 24	Day 30
TLC	8.3	9.19	7.99	8.32	11.57	7.41	6.57	7.77
Neutrophils	82.90	85.8	73.6	73.9	72.2	76.80	73.5	67.80
Lymphocytes	8.80	6.7	11.1	10.5	11.0	10.5	12.8	16.6
Eosinophils	0.70	1.1	10.9	8.2	8.6	3.9	6.70	3.7
Monocytes	7.00	6.0	4.3	6.90	7.3	8.4	6.50	11.1
Basophils	0.60	0.4	0.10	0.50	0.9	0.40	0.50	0.80

Since the patient continued to have fever after 15 days on Intravenous antibiotics, non-infectious causes of fever were also looked into. Differential diagnosis such as recurrence of PSH was considered. It was ruled out in the absence of other signs of sympathetic hyperactivity, such as tachycardia, sweating, dystonia, pupillary dilation, and an episodic presentation. Malignant hyperthermia and serotonin syndrome were ruled out

in view of lack of causative medication. Neuroleptic malignant syndrome too was excluded as other clinical features suggestive of the same were absent.

Based on a previous case report [7], the patient was started on Tab. Baclofen on day 19 of PMR stay, at a low dose of 5 mg twice daily. There was an immediate reduction in the temperature on the first day. Over the next 2 days, it was increased to 10 mg twice daily. This drastic improvement in the temperature was at a low dose of Baclofen. Incidental reduction in temperature coinciding with Baclofen administration was suspected and thus Baclofen was tapered and stopped over days, 23 and 24. The patient remained afebrile on day 25, but spiked a fever of 100°F the following day. On evaluation, TLC was found to be normal. Other features of prior hyperthermia such as absence of sweating and tachycardia were noted during this febrile episode as well.

Once baclofen was resumed, he continued to remain afebrile until discharge. Serial neurological examinations during the last week of hospital stay under PMR showed presence of spasticity in the left upper limb (elbow flexors and wrist flexors – Modified Ashworth Scale 1+) for which Baclofen was continued after discharge from the hospital, at a dose of 10 mg twice daily.

Fever monitoring during stay under PMR, and the dose of Baclofen administered is also described here (Figure 1).

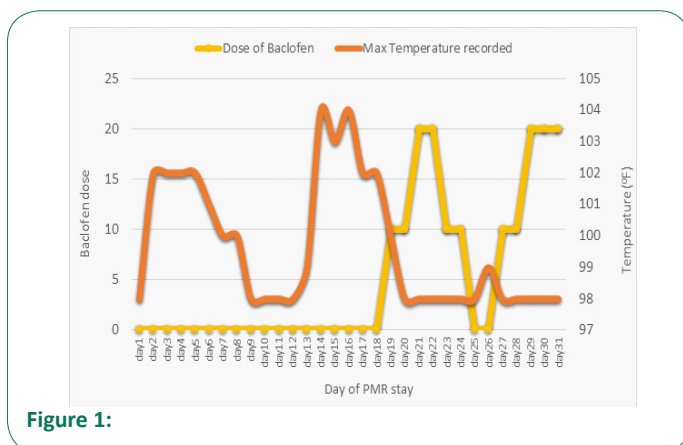


Figure 1:

## Discussion

This case brings to light the possible efficacy of low dose baclofen in the management of fever of central origin. It also highlights the unusual presentation of fever of non-infective etiology in the sub-acute stage after TBI.

Central fever has to be differentiated from other non-infective causes of fever such as Neuroleptic malignant syndrome, serotonin syndrome or Paroxysmal Sympathetic Hyperactivity (PSH) so as to prevent the use of unnecessary medication and unnecessary side effects and cost.

Fever of central origin is known to have a sudden onset, high grade temperatures, with inconsistent response to antipyretics. Fever has been shown to be an independent variable in patients with CNS injury and indicating poorer outcomes [8]. Compression of hypothalamic and brainstem thermoregulatory centers has been proposed as the cause for central hyperthermia [9]. In our patient, the contusions in the midbrain may have caused damage to the hypothalamus, but the late onset of central fever remains atypical.

Central fever is a diagnosis of exclusion. Since the body's thermoregulatory mechanism doesn't identify increased body

temperatures as abnormal, the regulatory responses such as sweating are absent or attenuated. The inconsistent response to antipyretics also points towards fever of central origin. Once an infective cause is ruled out, a patient with CNS conditions need to be evaluated for central fever.

In addition to external and internal cooling systems, studies have shown efficacy of drugs such as Bromocriptine [6] and Baclofen [7] in treating fever of central origin. The patient described here received antipyretics, external cooling devices and low dose baclofen.

Baclofen being a GABA agonist acts at raphe nuclei and inhibit brown adipose thermogenesis. This could be helpful in suppressing rising core body temperatures [10]. However, in an acute setting, side effect such as drowsiness or tiredness can limit its usage. On detecting hypothermia of central origin during rehabilitation setting, baclofen is a safe choice, unless the patient has prior history of seizures [11,12].

Another drug showing promise in the management of central hyperthermia is Bromocriptine. It is a D2 agonist that acts on the corpus striatum and hypothalamus. Supportive treatment strategies should be kept in mind during investigating and managing fever.

External cooling devices, although helpful in reaching normal body temperatures have been associated with skin breakdown [13]. Giving precooled IV fluids in a patient whom fluid overload can be tolerated has also been described as an effective way towards normothermia [13]. Both of the above has been shown to cause shivering. Literature on managing hyperthermia has been in the form of individual case reports and smaller studies [14].

## Conclusion

The case report describes the successful use of baclofen as an effective and rapid treatment for central hyperthermia in a patient with traumatic brain injury. Future studies to evaluate the efficacy and side effects of Baclofen in the management of central hyperthermia during acute and subacute period is warranted. Further controlled trials with adequate sample sizes are recommended to evaluate and standardize the use of baclofen and other such novel drugs in the management of central hyperthermia.

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